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Risk factors associated to kidney stones in primary hyperparathyroidism

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ABSTRACT. Nephrolithiasis is the most important clinical manifestation of primary hyperparathyroidism (PHPT), although nowadays this disorder is often asymptomatic. Clinical or biochemical differences between PHPT patients with and without nephrolithiasis have not been clearly identified in most of the previous studies. The aim of the study was to investigate clinical and biochemical parameters in kidney stone former (SF) and non-stone former (NSF) patients with PHPT in order to identify potential risk factors. Serum and plasma samples from 55 consecutive patients (43 females, 12 males) with PHPT were collected after overnight fasting; 24-h urine collection and a fresh sample of urine for sediment analysis were obtained from all patients. Clinical data were recorded in all. Out of 55 patients, 22 had kidney stones, which were symptomatic in 73%. SFs showed circulating PTH, total and ionized calcium, 1,25 dihydroxyvitamin D_3, urinary calcium excretion and 24-h urine oxalate levels significantly higher than NSFs. Hypercalciuria was often concomitant with massive quantities of calcium oxalate crystals in urine sediment. Hypercalciuria and relatively high oxaluria were associated with stone formation with an odds ratio (OR) of 4.0 and 7.0, respectively, which rose to 33.5 when they coexisted. Hypomagnesuria and hypocitraturia were common in at least one third of all PHPT patients, but they were not associated to an increased OR. As expected, they were positively correlated with urine calcium excretion, suggesting that calcium, magnesium and citrate are commonly regulated at renal level. In conclusion, hypercalciuria, higher oxalate excretion and severe PHPT are associated with kidney stones in PHPT.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is associated with increased risk of renal stones. Like patients with other types of calcium nephrolithiasis, PHPT patients are usually asymptomatic during the initial phase of stone formation, while severe acute renal colics may occur when the disease progresses. The clinical presentation of PHPT has shifted towards milder or asymptomatic features and the proportion of patients with nephrolithiasis tends to decrease in more recent series (1-4). Significant differences in clinical or biochemical parameters between PHPT patients with and without nephrolithiasis have not been clearly identified in most of the previous studies (2, 5-8). Several metabolic features have been proposed to induce kidney stone formation in PHPT. In particular, hypercalciuria, encountered in 18-40% of PHPT patients (2, 6, 7), has been associated with nephrolithiasis (2, 3). Relatively low levels of urinary magnesium, which is known to inhibit calcium oxalate crystallization by complexing oxalate, are also a common finding in PHPT patients with nephrolithiasis (9, 10). Renal citrate excretion, a natural urinary inhibitor of calcium salt crystallization and crystal growth, has been reported to be reduced in PHPT patients with kidney stones (11). Less conclusive data are available on other potential factors promoting kidney stone formation, such as dietary oxalate, hyperuricosuria and urine proteins, which have been linked to calcium oxalate crystal formation (12-17).

Key-words: Primary hyperparathyroidism, nephrolithiasis, hypercalciuria, oxaluria.

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The aim of the present study was to analyze several clinical and biochemical parameters in PHPT patients with and without nephrolithiasis, in order to identify clinical and biochemical background and risk factors for kidney stone development in PHPT.

MATERIALS AND METHODS

Subjects

We enrolled 55 consecutive patients [43 females and 12 males; median age at presentation 60 yr, interquartile range (IQR) 53-69] referred to our Institute between May 2000 and December 2001 for diagnosis and management of PHPT. Informed consent was obtained from all patients. Diagnosis of PHPT was made based on high ionized calcium levels in the presence of elevated or inappropriately normal serum PTH levels (ionized calcium 1.48 mmol/l, IQR 1.43-1.58; total serum calcium 2.69 mmol/l, IQR 2.58-2.82; serum PTH 118 pg/ml, IQR 74-155). No PHPT patient belonged to families with familial benign hypocalciuric hypercalcemia, as hypocalciuric patients did not show mutations in the DNA sequence analysis of the gene encoding the calcium sensing receptor. Thirty-three women out of 43 (77%) were in menopause, and 9 of them were being treated with hormone replacement therapy at the time of diagnosis. Hypertension was present in 62% (34 out of 55) of the patients. Antihypertensive therapy was modified in order to avoid administration of diuretics, with a wash-out period of at least one month.

Laboratory tests

Venous blood samples after an overnight fasting were obtained from all patients under a free diet for measurement of ionized calcium, total calcium, intact PTH, serum sodium and potassium, uric acid, glucose, creatinine, phosphate, magnesium, alkaline phosphatase with bone isoenzyme, 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3. Plasma ionized calcium was measured by a potentiometric method (Radiometer ABL System 625, Copenaghen, Denmark) on heparinized blood samples within 30 min from blood collection (reference limits: 1.15-1.29 mmol/l). Serum intact PTH was measured by a chemiluminescent method (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA); 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 were measured by RIA kit (Immunodiagnostic Systems Limited, Boldon, UK). Calcium, phosphate, magnesium, sodium, potassium, uric acid, protein, glucose and creatinine were also measured in 24-h urine collections (from 07:00 h of the day before to 07:00 h of the examination day). Urine oxalate and citrate concentrations were measured by enzymatic commercial kits (Sigma Diagnostics, St. Louis, MO, USA, and Boehringer Mannheim Gmbh, Biochemicals, Germany). Data obtained were checked at following controls. Fractional calcium excretion (FECa) was calculated as (UCa/UCr) x (SCr/SCa), where SCa is serum calcium in mg/dl, SCr is serum creatinine in mg/dl, UCa and UCr are urinary calcium and creatinine concentrations in mg/dl, respectively. A 2-h urine sample from the second urine of the morning was collected and prepared for microscope examination, as previously described (18). Crystals were examined by the same operator (F.G.B.) by a phase contrast microscope at 400x (high power field). Crystals were identified after their morphology and birefringence features and were semiquantitated from 0 to ++++. Microscopic hematuria was defined as >1 red blood cell/field at 400x (19). All patients underwent an ultrasound (US) examination of the urinary tract and suspicious imaging for stones were confirmed by X-ray. All had bone mineral density evaluation by dual energy X-ray absorptiometry (DEXA) of the lumbar spine L2-L4 and of the proximal femur (femoral neck).

Statistical analysis

Several variables in the study were not normally distributed. Therefore, we reported medians and IQR throughout the manuscript. We used the Wilcoxon rank-sum test or the Fisher's exact test for group comparisons of numerical and binary variables, respectively. We tested for linear correlation between variables by means of the Spearman rank correlation coefficient (r_s). We used Spearman's statistics because robust to the influence of outlier observations. In addition, all correlation analyses were repeated excluding possible points of leverage. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional multiple logistic regression. The ORs were adjusted for plasma ionized calcium and PTH levels. We considered results significant if p-value was <0.05. All statistical tests were two-sided. We performed all analyses using the Stata statistical package (Stata Corporation, College Station, TX, USA; release 7.0).

RESULTS

Clinical characteristics

Nephrolithiasis, defined as a history of renal colics with stone expulsions and/or imaging identification or asymptomatic US imaging of stones, was identified in 22 patients (40%), that were defined as stone formers (SFs). Sixteen SFs (73%) reported 1 to 6 episodes of renal colic and 11 (50%) reported previous stone expulsion. Half of SFs needed removal of stones either by surgery (3 patients) or by lithotripsy (8 patients). Nephrocalcinosis (US hyperecogenicity of a renal papilla) was identified in one patient, who had a recurrence of hyperparathyroidism. Only 2 patients did not recall any symptom and were diagnosed with microlithiasis by US imaging. Symptomatic stone disease (renal colic and stone expulsion) was recorded 13 yr (median; IQR 5-19 yr) before diagnosis of PHPT. No difference in age and sex distribution, frequency of estrogen deficiency and hypertension between SFs and non-stone formers (NSFs) was observed (Table 1). The median values of creatinine clearance were within the normal range in the two groups. Densitometry T-score, serum alkaline phosphatase levels and its specific bone isoenzyme were similar in SF and NSF patients.

Biochemical characteristics of stone former and non-stone former patients

Severity of PHPT

SF patients showed plasma ionized calcium, serum total calcium and PTH levels significantly higher than NSF patients, while serum phosphate and tubular maximal reabsorption of phosphate (TmP) were lower in SFs than NSFs (Table 2).

Table 1 – *Clinical and bone density characteristics of the primary hyperparathyroidism (PHPT) patients.*

	Stone formers	Non-stone formers
No.	22	33
Age (yr)	61 (53-67)[a]	54 (54-69)[a]
Female/Male	17/5	26/7
Estrogen deficiency (%)	62.5	60.0
Hypertension (%)	36	46
Renal function:		
creatinine clearance (ml/min)	86 (73-113)[a]	77 (63-103)[a]
urinary pH	5.8 (5.4-4.2)[a]	5.6 (5.4-6.2)[a]
Bone involvement:		
T-score >–1 (%)	6	10
-1> T-score >–2.5 (%)	47	45
T-score <–2.5 (%)	47	45
alkaline phosphatase (U/l)[b]	178 (160-286)[a]	185 (156-237)[a]
bone isoenzyme (%)[c]	78.4 (47.2-88.9)[a]	68.5 (51.6-80.0)[a]

Stone formers and non-stone formers did not differ for any of the parameters here described. [a]Median, interquantile range; [b]reference range: 98-279 U/l; [c]reference range: 40-60%.

Vitamin D status

We evaluated vitamin D_3 status in both groups of patients. Though 25-hydroxyvitamin D_3 levels did not differ significantly between SF and NSF patients (107.5, IQR 76-130 *vs* 102.5, IQR 62-126.3 nmol/l, respectively; normal range 23-113 nmol/l), SF patients showed 1,25-dihydroxyvitamin D_3 levels higher than NSFs (Table 2).

Renal calcium excretion

Hypercalciuria (urine calcium excretion > 4 mg/kg body weight/day) was present in 35 of 55 PHPT patients (63.6%) and it was significantly more frequent in SF (82%) than in NSF patients (52%; p=0.01). Twenty-four hour urine calcium excretion and FECa was were significantly higher in the SFs than in the NSFs (Table 2). Patients with hypercalciuria had

Table 2 – *Statistically significant differences in biochemical parameters between stone formers and non-stone formers primary hyperparathyroidism (PHPT) patients.*

	Normal	Stone formers (no.=22)		Non-stone formers (no.=33)		p
		Median	IQR	Median	IQR	
Ionized calcium (mmol/l)	1.15-1.29	1.56	1.47-1.72	1.45	1.41-1.54	0.002
Total calcium (mmol/l)	2.2-2.6	2.81	2.62-2.95	2.67	2.55-2.75	0.01
Intact PTH (pg/ml)	10-65	136.5	89-215	109	71-140	0.04
Serum phosphate (mmol/l)	0.8-1.5	0.71	0.58-0.77	0.84	0.68-0.98	0.003
TmP (mmol/l)	>0.9	0.48	0.41-0.56	0.59	0.47-0.70	0.02
$1,25(OH)_2D_3$ (pg/ml)	20-67	90.7	70.4-112.9	65.8	50.3-76.1	0.04
Urinary calcium (mg/kg/day)	<4	5.65	4.62-6.59	4.04	1.68-5.11	0.001
FECa	<0.01	0.025	2.0-2.9	0.02	0.012-0.026	0.009
Urinary oxalate (mg/24 h)	<40	24.2	18.7-37.1	16.8	9.6-28.5	0.01

IQR: interquartile range; TmP: tubular maximal reabsorption of phosphate; $1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3; FECa: fractional excretion of calcium.

Table 3A - *Relative odds for kidney stones in patients with hypercalciuria.*

Hypercalciuria*	NSFs	SFs	OR	(95% CI)	p-value	OR	(95% CI)	p-value
			Crude			Adjusted#		
No	18	4	1.0	-		1.0	-	
Yes	15	18	5.4	(1.5-19.5)	0.01	4.0	(1.0-15.9)	0.05

*Urine calcium higher than 4 mg/kg/24 h. #Adjusted for ionized calcium and PTH levels in multiple logistic regression analysis.
NSFs: non-stone formers; SFs: stone formers; OR: odds ratio; CI: interval of confidence.

Table 3B - *Relative odds for kidney stones in patients with high urine oxalate levels.*

Urine oxalate*	NSFs	SFs	OR	(95% CI)	p-value	OR	(95% CI)	p-value
			Crude			Adjusted#		
Low	20	5	1.0	-		1.0	-	
High	11	15	5.5	(1.6-19.1)	0.008	7.0	(1.7-28.8)	0.007

*Patients categorized using median urine oxalate excretion (19.8 mg/24 h) as the cut-off. #Adjusted for ionized calcium and PTH levels in multiple logistic regression analysis. NSFs: non-stone formers; SFs: stone formers; OR: odds ratio; CI: interval of confidence.

an OR for kidney stones of 4.0 (95% CI: 1.0-15.9; p=0.05) (Table 3A).

Renal oxalate excretion

Though the majority of patients had 24-h urine oxalate levels within the normal range (<40 mg/24 h) (20), urine oxalate excretion was significantly higher in SFs than in NSFs (Table 2). Urine oxalate excretion did not correlate with urine calcium excretion. Patients with 24-h urine oxalate value higher than the median value (19.8 mg/24 h) had an OR for kidney stones of 7.0 (95% CI: 1.7-28.8; p=0.007) (Table 3B). Patients with both relatively high oxaluria and hypercalciuria had a marked increase in the risk of kidney stones in comparison with patients without hypercalciuria and with low urine oxalate levels (OR: 33.5, 95% CI: 3.2-349; p=0.001). Interestingly, none of the SF patients was in the low-risk category, defined by the absence of both hypercalciuria and relative hyperoxaluria (Table 3C).

Other urine parameters

Hypomagnesuria (24-h urine excretion ≤75 mg/24 h) and hypocitraturia (<320 mg/24 h) were common features in about one third of both SF and NSF patients. Median 24-h urine magnesium and citrate levels in SF and NSF patients were similar. Moreover, both urine magnesium and citrate excretion were positively and significantly correlated with urine calcium excretion in both SF and NSF patients (Fig. 1), as described in healthy subjects. Hypomagnesuria and hypocitraturia were not associated with an increased OR for kidney stones in multiple regression analysis.
Urinary uric acid median levels were within the normal range in both groups. No significant difference be-

Table 3C - *Relative odds for kidney stones, by presence of hypercalciuria and/or higher urine oxalate levels.*

Hypercalciuria*	Urine oxalate^	NSFs	SFs	OR	(95% CI)	OR	(95% CI)
				Crude		Adjusted#	
No	Low	11	0	1.0	-	1.0	-
No	High	6	3	6.3	1.6-25.0	6.7	1.6-28.8
Yes	Low	9	5	7.9	1.7-36.8	5.0	0.9-27.8
Yes	High	5	12	49.4	5.1-483	33.5	3.2-349

*Urine calcium higher than 4 mg/kg/24 h. ^Patients categorized using median urine oxalate excretion (19.8 mg/24 h) as the cut-off. #Adjusted for ionized calcium and PTH levels in multiple logistic regression analysis.
NSFs: non-stone formers; SFs: stone formers; OR: odds ratio; CI: interval of confidence.

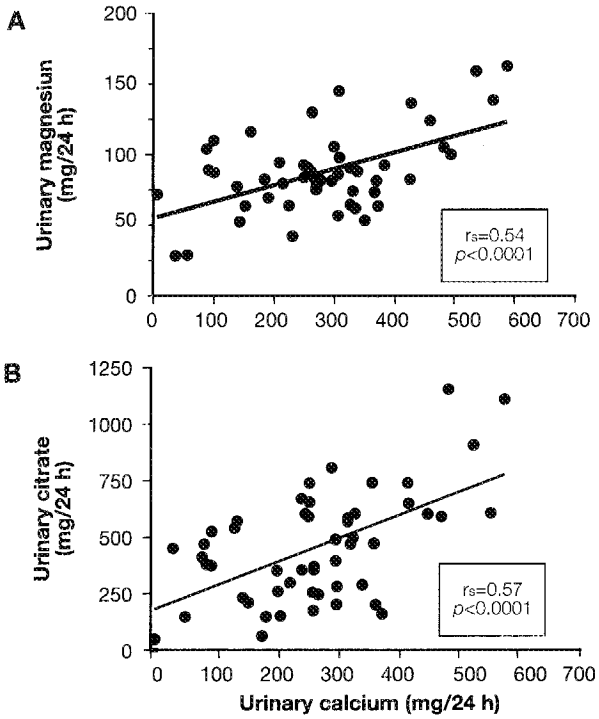

Fig. 1- *Positive correlations between urinary magnesium excretion (A), urinary citrate excretion (B) and urinary calcium excretion in all primary hyperparathyroidism (PHPT) patients. r_s: Spearman rank correlation coefficient.*

tween the two groups in urine pH, volume, sodium and potassium excretion, phosphate and protein excretion was found. Mild proteinuria (>0.2 g/24 h), in the absence of other causes of proteinuria, was found in 5 SF patients (25%) affected by severe PHPT (plasma ionized calcium and urine calcium ranging 1.59-2.2 mmol/l and 5.98-14.23 mg/kg/day, respectively). All NSF patients had urine protein excretion within the normal range.

Urinary sediment findings

The most frequent sediment abnormality was the presence of mild to massive quantities of calcium oxalate crystals, mainly dehydrated, that was detected in 32% of the SF patients and in 18% of the NSF patients (p=0.33). Both SFs and NSFs with calcium oxalate crystals were hypercalciuric (6.36 mg/kg/day, IQR 5.64-7.51 and 4.77 mg/24 h, IQR 3.46-5.10, respectively). Microscopic hematuria was found in 28% of SFs and 18% of NSFs and it was more severe in SFs than in NSFs (red blood cells ranging 5->100 high power field *vs* 2-10, respectively). In all cases, hematuria was isomorphic suggesting a non-glomerular origin. However, no significant difference between SF and NSF patients in urinary sediment characteristics was observed.

DISCUSSION

The data presented confirm that nephrolithiasis remains a frequent and important complication in PHPT. In our series, kidney stones affected 40% of the patients with PHPT, a percentage close to previous studies (2, 5, 7, 8), but higher than that reported by more recent studies characterized by a high prevalence of asymptomatic PHPT (21, 22). Indeed, in the present study all patients were screened by US or Rx imaging of the kidneys to identify also asymptomatic renal stone disease. Nonetheless, renal stone disease was symptomatic in most patients with a delayed time of a decade from the first stone episode to PHPT diagnosis and interventional treatment was required in half the symptomatic patients. This observation is in line with a previous report showing that PHPT patients had a greater risk of renal stone disease even 10 yr before the diagnosis was registered (23).

Since the pathogenesis of stone formation in PHPT remains unclear, the present study evaluated a number of previously supposed risk factors for stone development. The patients were studied on a free diet and the dietary habitus, indirectly estimated by the evaluation of the 24-h urine volume and salt concentrations, was similar in both groups. No significant differences in urinary uric acid, magnesium and citrate levels between SFs and NSFs were observed, though hypomagnesuria and hypocitraturia were common in at least one third of all PHPT patients. The data presented support a central role for hypercalciuria in kidney stone development in hyperparathyroid patients, as previously suggested (24). Hypercalciuria more frequently occurred in SF patients, though at least half of NSF patients had elevated renal calcium excretion. In SF patients urine calcium excretion was significantly more massive than in NSF patients and this feature appears associated with a more severe PHPT in SF patients, though clinical features, including bone involvement, were similar. In fact, in SFs circulating ionized and total calcium as well as PTH levels were higher and serum phosphate and TmP values lower than in NSF patients. These data are in agreement with the report by Söreide et al. (3), while other surgical series described similar severity of the PHPT between SFs and NSFs (23, 25). However, it should be considered that surgical series most likely included patients with severe PHPT.

Patients with mild to massive quantities of calcium oxalate crystals in urine sediments were hypercalciuric, while mild proteinuria and consistent microhematuria were frequently observed in severe hypercalciuric SF patients. Moreover, in our series, as in normal subjects, urine calcium excretion was positively correlated with urine magnesium and

citrate excretions, supporting the hypothesis that renal calcium, magnesium and citrate excretions result from common events at the renal tubular levels. Finally, while we failed to identify an increased risk associated to hypomagnesuria and hypocitraturia, hypercalciuria was associated with a 4-fold increased risk to develop kidney stones.

The calcium excess in the urine may result from either enhanced intestinal calcium absorption, increased mobilization of skeletal calcium, or increased urinary excretion. Increased renal production of calcitriol with hyperabsorption of intestinal calcium is believed to be clinically important (26, 27). Although SF and NSF patients did not differ in 25-hydroxyvitamin D_3 levels, we found higher 1,25-dihydroxyvitamin D_3 levels in SF than in NSF patients, in line with some previous reports (26, 27). However, the lack of any significant correlation between 1,25-dihydroxyvitamin D_3 levels, serum calcium and PTH levels and urine calcium excretions suggests that vitamin D status was not the main determinant of hypercalcemia and hypercalciuria in these patients. The reduction in renal calcium reabsorption may contribute to hypercalciuria, as suggested by the observation that the FECa was higher in SF patients compared to NSF patient.

Urine oxalate has been recognized as a kidney stone promoter in PHPT (15) and, interestingly, in the present study SF patients showed 24-h urine oxalate concentrations higher than NSFs. Moreover, in a rat model of hyperoxaluria animals excreted calcium oxalate dihydrate crystals (28), as observed in our series. In this setting, patients with 24-h urine oxalate higher than the median value had a 7.0-fold increase in the probability of kidney stones. Accordingly, patients with both hypercalciuria and higher urine oxalate excretion showed a 30-fold increase in the relative OR for kidney stones. These findings support the recommendations by the recent Statement from the workshop on asymptomatic PHPT (29). The Panel of experts emphasized the importance of urine oxalate excretion as a contributor to stone formation and recommended a baseline assessment of urinary calcium excretion as a general measure of the renal burden for handling calcium.

When it is not genetically determined, hyperoxaluria is due to excessive intestinal absorption. High levels of 1,25-dihydroxyvitamin D_3 in SF patients might induce high calcium and consequently oxalate intestinal absorption, as hyperabsorption of calcium may enhance the intestinal uptake of free oxalate (30, 31). Alternatively, recent reports highlighted the role of enteric *Oxalobacter formigens*, an intestinal oxalate degrading bacterium, in maintaining oxalate homeostasis, since its absence from the gut may lead to increased intestinal oxalate absorption (32, 33). Therefore, accurate evaluation of oxalate metabolism in PHPT patients may provide further insight in the identification of kidney stones risk factors.

In conclusion, the present study showed that high urine calcium and oxalate excretions were strongly associated with kidney stone disease in PHPT patients and indicates the need for the evaluation of these parameters in these patients.

REFERENCES

1. Chan AK, Duh Q-Y, Katz MH, et al. Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy. Ann Surg 1995, 222: 402-14.
2. Silverberg SJ, Shane E, Jacobs TP, et al. Nephrolithiasis and bone involvement in primary hyperparathyroidism. Am J Med 1990, 89: 327-34.
3. Söreide JA, van Heerden JA, Grant CS, Lo CY, Ilstrup DM. Characteristics of patients surgically treated for primary hyperparathyroidism with and without renal stones. Surgery 1996, 120: 1033-7.
4. Udèn P, Chan A, Duh Q-Y, et al. Primary hyperparathyroidism in younger and older patients: symptoms and outcome of surgery. World J Surg 1992, 16: 791-8.
5. Purnell DC, Smith LH, Scholz DA, Elveback LR, Arnaud CD. Primary hyperparathyroidism: a prospective clinical study. Am J Med 1971, 50: 670-8.
6. Broadus A. Nephrolithiasis in primary hyperparathyroidism. In: Coe F, Brenner B, Stein J eds. Nephrolithiasis. New York: Chirchill Livingstone. 1980.
7. Pak CY, Nicar MJ, Peterson R, Zerwekh JE, Snyder W. A lack of unique pathophysiologic background for nephrolithiasis of primary hyperparathyroidism. J Clin Endocrinol Metab 1981, 53: 536-42.
8. Kristoffersson A, Backman C, Granqvist K, Jarhult J. Pre- and postoperative evaluation of renal function with five different tests in patients with primary hyperparathyroidism. J Int Med 1990, 227: 317-24.
9. Sutton RA, Watson L. Urinary excretion of calcium and magnesium in primary hyperparathyroidism. Lancet 1969, 1: 1000-3.
10. Johannson G, Danielson BG, Ljunghall S. Magnesium homeostasis in mild to moderate primary hyperparathyroidism. Acta Chirur Scand 1980, 146: 85-91.
11. Alvarez-Arroyo MV, Traba ML, Rapado A, de la Piedra C. Role of citric acid in primary hyperparathyroidism with renal lithiasis. Urol Res 1992, 20: 88-90.
12. Lonsdale K. Human stones. Science 1968, 159: 1199-207.
13. Pak CYC, Holt K, Zerwekh JK. Attenuation by sodium urate of the inhibitory effect of glycosaminoglycans on calcium oxalate nucleation. Invest Urol 1979, 17: 138-41.
14. Ljunghall S, Akerstrom G. Urate metabolism in primary hyperparathyroidism. Urol Intern 1982, 37: 73-8.
15. Baumann JM, Lauber K, Lustenberger FX, Wacker M, Zingg EJ. Crystallization conditions in urine of patients with idi-

opathic recurrent calcium nephrolithiasis and with hyperparathyroidism. Urol Res 1985, 13: 169-74.

16. Atmani F, Khan SR. Quantification of proteins extracted from calcium oxalate and calcium phosphate crystals induced in vitro in the urine of healthy controls and stone forming patients. Urol Intern 2002, 68: 54-9.
17. Broulek PD, Stepan JJ, Pacovsky V. Primary hyperparathyroidism and hyperuricemia are associated but not correlated with indicators of bone turnovers. Clin Chim Acta 1987, 170: 195-200.
18. Fogazzi GB, Ponticelli C, Ritz E. The urinary sediment. An integrated view. 2nd ed. Oxford: Oxford University Press. 1999: 13-28.
19. Fogazzi GB, Ponticelli C. Microscopic haematuria, diagnosis and management. Nephron 1996, 72: 125-34.
20. Sutton RA, Walker VR. Enteric and mild hyperoxaluria. Min Electrolyte Metab 1994, 20: 352-60.
21. Bilezikian JP, Silverberg SJ, Shane E, Parisien M, Dempster DW. Characterization and evaluation of asymptomatic primary hyperparathyroidism. J Bone Min Res 1991, Suppl 2: S85-89.
22. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Eng J Med 1999, 341: 1249-55.
23. Mollerup CL, Vestergaard P, Frøkjaer VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stones events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. Br Med J 2002, 325: 807-11.
24. Coe FL, Parks JL, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med 1992, 327: 1141-52.
25. Frøkjaer VG, Mollerup CL. Primary hyperparathyroidism: renal calcium excretion in patients with and without renal stone disease before and after parathyroidectomy. World J Surg 2002, 26: 532-5.
26. Broadus AE, Horst RL, Lang R, Littledike ET, Rasmussen H. The importance of circulating 1,25-dihydroxyvitamin D in the pathogenesis of hypercalciuria and renal-stone formation in primary hyperparathyroidism. N Engl J Med 1980, 302: 421-6.
27. Patron P, Gardin JP, Poullard M. Renal mass and reserve of vitamin D: determinants in primary hyperparathyroidism. Kidney Int 1987, 31: 1176-80.
28. Marengo SR, Chen DH, MacLennan GT, Resnick MI, Jacobs GH. Minipump induced hyperoxaluria and crystal deposition in rats: a model for calcium oxalate urolithiasis. J Urol 2004, 171: 1304-8.
29. Bilezikian JP, Potts JT, Fuleihan GE, et al. Summary Statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002, 87: 5353-61.
30. Giannini S, Nobile M, Castrignano R, et al. Possibile link between vitamin D and hyperoxaluria in patients with renal stone disease. Clin Sci (London) 1993, 84: 51-4.
31. Krishnamurthy MS, Hruska KA, Chandhoke PS. The urinary response to an oral oxalate load in recurrent calcium stone formers. J Urol 2003, 169: 2030-3.
32. Kwak C, Kim HK, Kim EC, Choi MS, Kim HH. Urinary oxalate levels and the enteric bacterium Oxalobacter formigenes in patients with calcium oxalate urolithiasis. Eur Urol 2003, 44: 475-81.
33. Hoppe B, Leumann E, von Unruh G, Laube N, Hesse A. Diagnostic and therapeutic approaches in patients with secondary hyperoxaluria. Front Biosci 2003, 8: e437-43.